PART I - THE SYNTHESIS OF SOME FLUORO SUBSTITUTED CARCINOGENIC COMPOUNDS.

PART II - THE SYNTHESIS OF SOME CYCLIC IODONIUM SALTS.

PART III - THE HAYASHI REARRANGEMENT OF o-BENZOYLBENZOIC ACIDS.

by

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All melting points are uncorrected

PART 1

THE SYNTHESIS OF SOME FLUORO SUBSTITUTED CARCINOGENIC COMPOUNDS

INTRODUCTION

In the past fifty years a large number of chemical compounds which produce cancers have been synthesized. The accumulated information about these compounds has greatly increased our knowledge about the carcinogenic process. However, much is still to be learned. There are two main classifications of carcinogenic compounds. These are polycyclic aromatic hydrocarbons, and dyes related to azobenzene.

Numerous studies have been made on the dye, dimethylamino azobenzene (D.A.B.) and related compounds, to determine factors necessary for carcinogenic activity[1]. It has been found that altering the linkage between the two benzene nuclei usually removes the activity completely. The activity is also modified considerably by the introduction of ring substituents. Methyl- and chloro- derivatives change the activity only slightly. Hydroxy-, methoxy- and nitro- derivatives show greatly decreased activity, but fluoro- derivatives show increased activity in almost all cases[2]. Polysubstitution removes the activity in all cases except when fluorine is the substituent.

The increased activity of the fluoro-substituted D.A.B. may be due to the fact that fluorine is highly electronegative but does not differ greatly from hydrogen in atomic volume. Thus fluorine contributes to the resonance system without introducing added strain in the molecule. A second reason why fluoro-substituted D.A.B. shows increased activity may be because of the strength of the carbon-fluorine bond. Chemical compounds are metabolized usually by hydroxylation, thus rendering the compounds soluble in the body fluids. In this way compounds are removed as wastes. Replacement of fluorine by the hydroxyl group requires strong alkali and a long reflux period. The presence of substituted fluorine may therefore interfere with or slow the metabolic process and thus increase the chance for tumor production.

Many derivatives of benz[a]anthracene show carcinogenic activity although the hydrocarbon itself does not. Benz[a]anthracene is metabolized to give 4-hydroxybenz[a]anthracene. It is believed however that metabolism proceeds through the intermediate formation of the 3,4-dihydroxy-3,4-dihydrobenz[a]anthracene[3], and thus the 3 position must be available for attack.

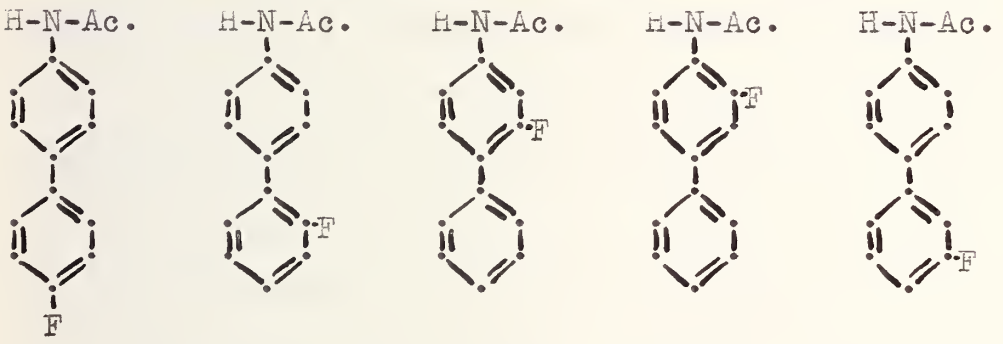
Several fluoro-substituted carcinogens have therefore been prepared so that the importance of fluorine

substitution can be evaluated. These include 4-acetylamino-2-fluorobiphenyl, 4-acetylamino-3-fluorobiphenyl, 4-acetylamino-3'-fluorobiphenyl, and 2- and 3-fluorobenz[a]anthracene. A known carcinogen, 2-acetylaminophenanthrene was also prepared by a new procedure.

MONOFLUORO-4-ACETYLAMINOBIPHENYLS

Figure 1 shows the five mono-fluoro derivatives of 4-acetylaminobiphenyl.

Figure 1



I II III IV V

Van Hove[4] prepared I by the nitration of 4-fluorobiphenyl followed by reduction and acetylation. This same procedure was used by A. Hay in this laboratory.

F. Chubb of this laboratory prepared II by a Beckmann rearrangement of the oxime of 4'-acetyl-2-fluorobiphenyl. The 4'-acetyl-2-fluorobiphenyl was prepared by the acetylation of 2-fluorobiphenyl[5]. Chubb also prepared II by the nitration of 2-fluorobiphenyl followed by reduction and acetylation[4]. A mixed melting point of the two products showed no depression.

Van Hove[4] also reported the preparation of III by the nitration of 2-fluorobiphenyl followed by reduction and acetylation. Zahn and Auber[6] however have

shown that nitration of 2-fluorobiphenyl gives 2-fluoro-2',3,4',5-tetranitrobiphenyl. The compound van Hove reported as III was probably 5-acetylamino-2-fluorobiphenyl.

An attempt to prepare III by the nitration of 4'-acetyl-2-fluorobiphenyl followed by oxidation of the acetyl group to a carboxyl group and then decarboxylation failed, as only dinitration could be accomplished. Decarboxylation of the acid prepared from the product of the nitration reaction proved unsucessful. The positions of nitration were never determined but from the results obtained by Zahn and Zuber[6], they would probably be the 2' and 5 positions.

III was finally prepared by the synthesis route illustrated in figure II.

The nitration of benzidene[7] and the following steps to the formation of 4-amino-2-nitrobiphenyl[8] are reported in the literature. A certain amount of difficulty was encountered in the Schiemann reaction in the last step, as the diazonium fluoborate formed was very soluble in the usual liquids used for washing (methanol, ethanol and dioxane). Isopropyl alcohol was found to be a satisfactory intermediate wash liquid between water and ether. The decomposition of the diazonium fluoborate occurred in a yield of only 10%.

Figure II

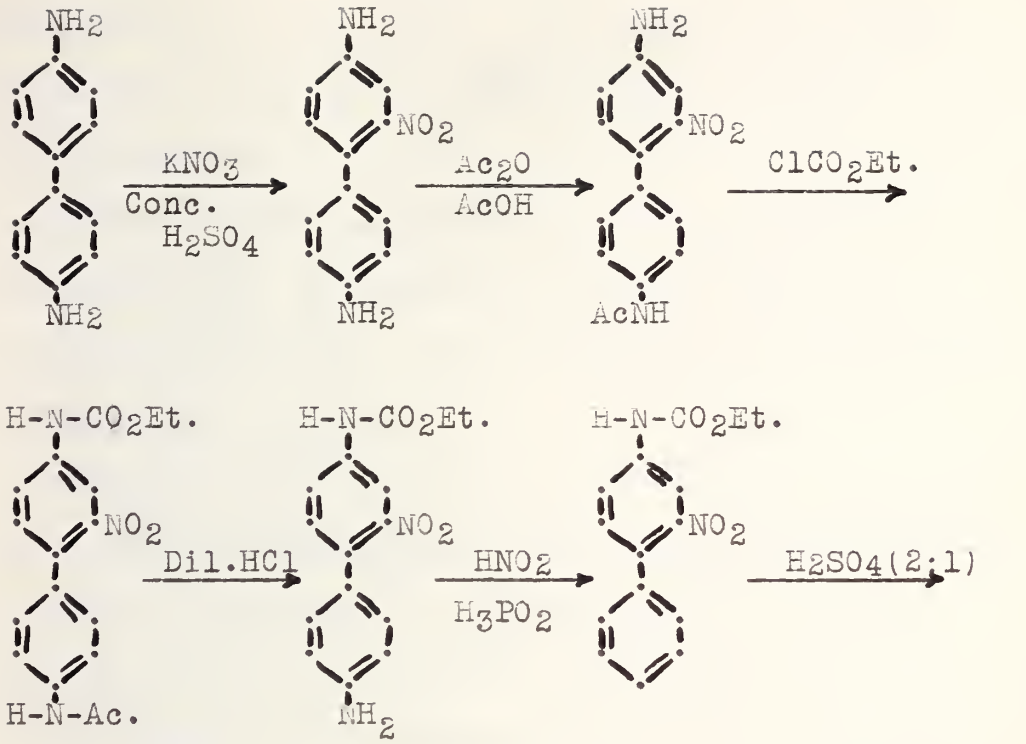
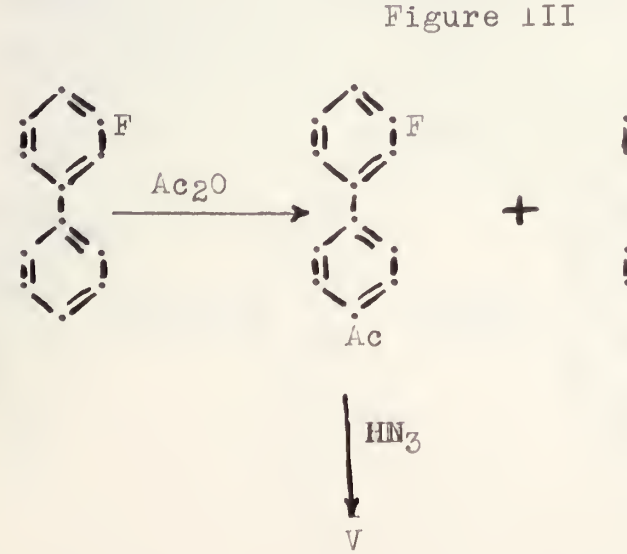


Figure III

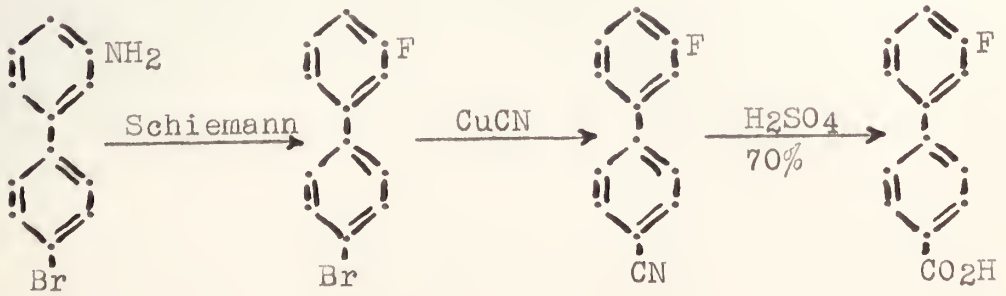


III prepared in this manner melted 10° below that reported by van Hove[4]. The compound reported by van Hove to be III is probably 5-acetylamino-2-fluorobiphenyl.

IV and V were prepared by the acetylation of 3-fluorobiphenyl followed by a Schmidt reaction of the resulting ketones. This synthesis is illustrated in figure III.

3-Aminobiphenyl was prepared by a five step synthesis from 4-aminobiphenyl, first reported by F. Fichter and A. Sulzberger[9]. 3-fluorobiphenyl is also reported in the literature[10]. The acetylation of 3-fluorobiphenyl was a modification of the procedure Kenoll[5] used on 2-fluorobiphenyl. The products of the acetylation had not been previously reported in the literature and were characterized by Chubb in the following ways. Oxidation of 4'-acetyl-3-fluorobiphenyl with permanganate gave 3-fluoro-4'-biphenylcarboxylic acid which was also prepared by the series shown in figure IV.

Figure IV

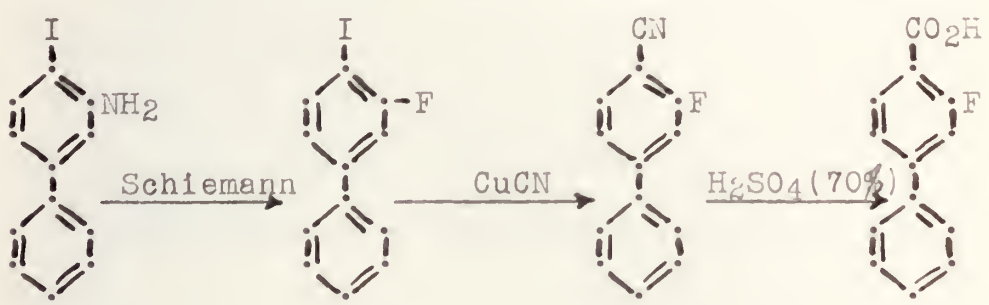


3-Amino-4'-bromobiphenyl was prepared from 3-nitrobiphenyl[11]. The 3-fluoro-4'-biphenylcarboxylic acid thus formed proved by mixed melting point to be identical with that prepared from 4'-acetyl-3-fluorobiphenyl.

Oxidation of 4-acetyl-3-fluorobiphenyl with permanganate gave 3-fluoro-4-biphenylcarboxylic acid which was also prepared by the series shown in figure V.

4-Iodo-3-nitrobiphenyl is reported by Hodgson and Walker[12]. The 3-fluoro-4-biphenylcarboxylic acid thus formed proved by mixed melting point to be identical with that prepared from 4-acetyl-3-fluorobiphenyl. Identical amides were prepared from the two acids.

Figure V



EXPERIMENTAL

4'-Acetylamino-3-fluorobiphenyl and 4-Acetylamino-3-fluorobiphenyl

4-Acetylaminobiphenyl. -Thirty-six grams of 4-aminobiphenyl was dissolved at 50° in 500 ml. of water and 16.6 ml. of concentrated hydrochloric acid. To this solution was added 23.3 ml. of acetic anhydride, and sodium acetate(18 g. in 100 ml. of water). The solution was stirred for 30 minutes, cooled and filtered giving an almost quantitative yield of 4-acetylaminobiphenyl, m.p. 170-172°.

4-Acetylamino-3-nitrobiphenyl. - Ninety grams of crude 4-acetylaminobiphenyl was dissolved in 900 ml. of acetic acid and 110ml. of acetic anhydride was added. The solution was warmed to 70° and 50 ml. of concentrated nitric acid in 50 ml. of acetic acid was added slowly. The mixture was kept at 70° for 30 minutes and then diluted with 4.5 liters of water. The crude 4-acetylamino-3-nitrobiphenyl was filtered, washed with water and recrystallized from alcohol. The yield of 4-acetylamino-3-nitrobiphenyl was 87 g.(80%), m.p. 129-131°.[9]

4-Amino-3-nitrobiphenyl. - Five grams of 4-acetylamino-3-nitrobiphenyl was dissolved in a solution of 5 g. of potassium hydroxide, 5 ml. of water and 40 ml. of alcohol by warming. On standing, the red

product precipitated. The yield of 4-amino-3-nitrobiphenyl was 4 g. (95%), m.p. 168-169°.[9]

3-Nitrobiphenyl. - Forty-three grams of 4-amino-3-nitrobiphenyl was added to a solution of 40 ml. of concentrated sulfuric acid in 400 ml. of alcohol. The mixture was cooled to 5° in an ice bath and 40 ml. of isoamyl nitrite was added slowly with stirring. After about three quarters of the isoamyl nitrite had been added the yellow diazonium salt precipitated and the mixture became very thick. Another 200 ml. of alcohol was added and the rest of the isoamyl nitrite was slowly added to the solution. The end of the reaction was indicated by complete disappearance of the red color of the 4-amino-3-nitrobiphenyl.

The mixture was transferred to a 2-l. flask, fitted with a reflux condenser, and slowly heated to boiling. After the evolution of nitrogen had ceased, most of the alcohol was distilled. The residue from the distillation was dissolved in ether, washed with water and dried with anhydrous sodium sulfate. The ether was evaporated and the residue distilled. The yield of 3-nitrobiphenyl was 36 g. (90%), b.p. 195-200° at 20 mm., m.p. 58-60°[9]

3-Aminobiphenyl. - Fifty-five grams of 3-nitrobiphenyl was partially dissolved in 250 ml. of alcohol and was reduced over 5 g. of Raney nickel with hydrogen at 40 p.s.i. The Raney nickel was filtered and the filtrate was distilled under reduced pressure. The yield of 3-aminobiphenyl was 43 g. (92%), b.p. 185-190° at 20 mm.

3-Biphenyldiazonium Fluoborate. - Nineteen grams of 3-aminobiphenyl was dissolved in 100 ml. of alcohol and 100 ml. of fluoboric acid solution. The solution was cooled to 5° and 24 ml. of isoamyl nitrite was added dropwise. After a few minutes the diazonium fluoborate separated as yellow plates. The product was filtered and washed with cold alcohol and cold ether. The yield of 3-biphenyldiazonium fluoborate was 26 g.(87%) decomposition point 87° [10].

3-Fluorobiphenyl. - Fifty-two grams of 3-biphenyldiazonium fluoborate was decomposed in a flask in the usual manner, by heating the dry salt. The liquid residue was dissolved in ether, washed with 10% sodium hydroxide and water and dried over anhydrous sodium sulfate. The product was distilled under reduced pressure. The yield of 3-fluorobiphenyl was 19 g. (54%), b.p. 130-135° at 20 mm. [10].

Acetylation of 3-Fluorobiphenyl. - In a 500 ml. 3-necked flask fitted with a mechanical stirrer, dropping funnel and a reflux condenser connected to a gas trap, was placed 50 g. of 3-fluorobiphenyl, 117 ml. of carbon disulfide and 88 g. of anhydrous aluminum chloride. The flask was heated on a water bath until gentle refluxing began. Twenty-four grams of acetic anhydride was added through the dropping funnel during the space of one hour. The mixture was then refluxed for another hour.

Part of the solvent was distilled and the residue was allowed to cool. It was then poured into an ice-hydrochloric acid mixture. The product was extracted 3 times with ether and the combined ether extracts were washed with water, 10% sodium hydroxide and water.

After drying over anhydrous sodium sulfate and evaporation of the ether, the product was distilled giving 14 g. b.p. 110-160° and 28 g. b.p. 180-190° at 2-3 mm. The lower fraction was poured into 50 ml. of ligroin and 1.4 g. of 4-acetyl-3-fluorobiphenyl precipitated. The soluble portion was mainly 3-fluorobiphenyl.

The higher boiling fraction when crystallized twice from alcohol gave 13 g. of 4-acetyl-3-fluorobiphenyl, m.p. 102-103°.

Anal. Calcd. fo $C_{14}H_{11}OF$: C, 78.50; H, 5.18. Found: C, 78.14; H, 5.32.

Oxime of 4-acetyl-3-fluorobiphenyl had an m.p. of 143-144°.

Anal. Calcd for $C_{14}H_{12}ONF$: C, 73.31; H, 5.24. Found: C, 73.49; H, 5.18.

Concentration of the mother liquors from the above crystallization gave 11 g. of product, m.p. 73-78°. This was converted to the oxime for further purification.

Oxime of 4'-Acetyl-3-fluorobiphenyl. - Eleven grams of crude 4'-acetyl-3-fluorobiphenyl was heated with 5.5 g. of hydroxylamine sulfate, 5.5 g. of sodium hydroxide, 50 ml. of water and 25 ml. of alcohol. After solution of the ketone was complete, 5 ml. of concentrated hydrochloric acid was added and the oxime precipitated. Recrystallization from alcohol yielded 7 g. of the oxime of 4'-acetyl-3-fluorobiphenyl, m.p. 152.5-154°.

Anal. Calcd. for $C_{14}H_{12}ONF$: C, 73.31; H, 5.24. Found: C, 73.31; H, 5.58.

4'-Acetyl-3-fluorobiphenyl. - Twenty grams of the oxime of 4'-acetyl-3-fluorobiphenyl was dissolved in 100 ml. of alcohol and 100 ml. of concentrated hydrochloric acid was added. The solution was refluxed for one hour. An additional 100 ml. of acid was added and the refluxing was continued for thirty minutes. The solution was cooled, ex-

tracted with ether and the ether extract was washed with water, 10% sodium hydroxide and water. The ether was dried with anhydrous sodium sulfate and evaporated to give 19 g. of 4'-acetyl-3-fluorobiphenyl, m.p. 71-75°. Recrystallization from alcohol gave an analytical sample, m.p. 90-91°.

Anal. Calcd. for $C_{14}H_{11}OF$: C, 78.50; H, 5.18. Found: C, 78.35; H, 5.10.

4'-Acetylamino-3-fluorobiphenyl. - Nineteen grams (.09 mole) of 4'-acetyl-3 -fluorobiphenyl was dissolved in 200 ml. of benzene and 25 ml. of concentrated sulfuric acid. To this solution was added 100 ml. of 1.45 M. hydrazoic acid in benzene solution. The solution was stirred for 1 hour and then the reaction was allowed to stand over night.

The product was extracted with ether and the ether extract was washed with water, 10% sodium hydroxide and water, and dried over anhydrous sodium sulfate. The ether was removed by evaporation, and the product was crystallized from benzene. The yield of 4'-acetylamino-3-fluorobiphenyl was 13 g. (65%), m.p. 180-181°.

Anal. Calcd. for $C_{14}H_{12}ONF$: C, 73.31; H, 5.24; Found: C, 73.51; H, 5.45.

4-Acetylamino-3-fluorobiphenyl. - The same procedure was used as for the preparation of 4'-acetylamino-3-fluorobiphenyl. The product was recrystallized from 60% alcohol. The yield of 4-acetylamino-

3-fluorobiphenyl was 65%, m.p. 142-143°.

Anal. Calcd. for $C_{14}H_{12}ONF$: C, 73.31; H, 5.28. Found: C, 72.86; H, 5.54.

4-Acetylamino-2-fluorobiphenyl

4'-Acetylamino-4-amino-2-nitrobiphenyl. - To a solution of 40 g. of 2-nitrobenzidine in 360 ml. of boiling alcohol was added 360 ml. of hot water at 60° and 17 ml. of acetic anhydride. The solution was refluxed for 10 minutes, and then treated with 360 ml. of cold water and cooled. The mixture of crystallized mono- and di-acetyl compounds was dissolved in 500 ml. of boiling acetone. Most of the diacetyl remained undissolved and was filtered. Evaporation of the acetone gave a residue which when crystallized from alcohol yielded 50 g. of 4'-acetylamino-4-amino-2-nitrobiphenyl, m.p. 202-204° [8].

4'-Acetylamino-4-carbethoxyamino-2-nitrobiphenyl. Twenty grams of the monoacetyl compound was dissolved in 250 ml. of boiling alcohol and treated with 16 ml. of diethylaniline and then dropwise with 8 ml. of ethyl chloroformate. After the vigorous reaction had subsided, the solution was refluxed for 10 minutes, filtered and allowed to cool. Twenty grams of the urethane crystallized in yellow prisms which melted at 210-212° [8].

4'-Amino-4-carbethoxyamino-2-nitrobiphenyl. - Twenty grams of the urethane was refluxed for 2.5 hours in 270 ml. of alcohol and 30 ml. of concentrated hydrochloric acid. The hydrochloride salt of the amine

began separating after 2 hours. Dilution of the hot reaction mixture with water and neutrallization with alkali precipated 15 g. of the amine. Recrystallization from alcohol gave 12.5 g. of 4'-amino-4-carbethoxyamino-2-nitrobiphenyl, m.p. 174-175° [8].

4-Carbethoxyamino-2-nitrobiphenyl. - Twenty grams of the amine was dissolved in 600 ml. of boiling alcohol, the solution was cooled to 40° and treated with 10 ml. of concentrated sulfuric acid. A sparingly soluble sulphate precipitated at first but then redissolved. The solution was cooled rapidly to 20° and 7 g. of sodium nitrite in 120 ml. of water was added with stirring. After 10 minutes, 40 ml. of 30% hypophosphorous acid was added and stirring was continued for 4 hours. Addition of water precipitated the crude product which was extracted with benzene washed with sodium hydroxide, water, dilute sulfuric acid and water. The dried solution was evaporated to give 15 g. of 4-carbethoxy-2-nitrobiphenyl, m.p. 120° [8].

4-Amino-2-nitrobiphenyl. - Five grams of 4-carbethoxyamino-2-nitrobiphenyl was dissolved in 10 ml. of sulfuric acid and 5 ml. of water and the solution was heated at 150° for 5 minutes after bubbles of carbon dioxide had stopped(about 40 minutes). The solution was poured into water and basified. The free base was extracted with benzene, washed with water and dried

with anhydrous sodium sulfate.

An analytical sample of 4-amino-2-nitrobiphenyl, m.p. 106-107° was prepared by evaporation of the benzene and crystallization of the residue from 50% alcohol.

Anal. Calcd. for $C_{12}H_{10}O_2N_2$: C, 67.27; H, 4.70. Found: C, 67.17; H, 4.73.

4-Acetylamino-2-nitrobiphenyl. - The benzene solution of 4-amino-2-nitrobiphenyl from above was evaporated to 30 ml. To the hot solution was added 2.5 ml. of acetic anhydride. After boiling for 5 minutes the product precipitated. On cooling, the mixture was filtered giving a quantitative yield of 4-acetylamino-2-nitrophenyl, m.p. 186-187.5°.

Anal. Calcd. for $C_{14}H_{12}O_3N_2$: C, 65.60; H, 4.74. Found: C, 65.74; H, 4.66.

4-Acetylamino-2-aminobiphenyl. - Five grams of 4-acetylamino-2-nitrobiphenyl was dissolved in 150 ml. of hot methanol and was reduced over Raney nickel at a hydrogen pressure of 40 p.s.i. Reduction was complete in .5 hour. The Raney nickel was filtered and the methanol was evaporated to give a thick syrup which was distilled with much loss to give a colorless syrup, b.p. 210° at .4 mm. The syrup crystallized on standing several months. It could also be crystallized with difficulty from benzene to give 4-acetylamino-2-amino-

biphenyl, m.p. 76-77°. The best analysis obtained on this compound was as follows;

Anal. Calcd. for $C_{14}H_{14}ON_2$: C, 74.28; H, 6.23. Found: C, 76.68; H, 6.34.

The hydrochloride of 4-acetylamino-2-aminobiphenyl was prepared by dissolving the amine in dioxane and adding dry hydrogen chloride. A quantitative yield of the hydrochloride salt precipitated and was filtered, m.p. 175°.

Anal. Calcd. for $C_{14}H_{15}ON_2Cl$: Cl,
Found: Cl,

4-Acetylamino-2-fluorobiphenyl. - Eight grams of 4-acetylamino-2-aminobiphenyl was dissolved in a fluoboric acid solution(20 g. of 40% hydrofluoric acid, 7.5 g. of boric acid and 50 ml. of water). To this solution at 10° was added dropwise 15 ml. of 20% sodium nitrite solution. After about half of the sodium nitrite solution had been added, the diazonium fluoborate began to precipitate. The addition was completed and the solution was stirred for an additional 30 minutes. The yellow precipitate was filtered, washed with cold water, cold isopropyl alcohol and cold ether, and dried to give 8 g. of 4-acetylamino-2-biphenyldiazonium fluoborate, decomposition point 72°.

The diazonium fluoborate was decomposed thermally to give a thick tar. This tar was dissolved in acetone

and ether. Addition of water gave another layer and much tar. The ether solution was washed with water, sodium hydroxide and water, and was dried with sodium sulfate. Evaporation of the ether gave a tar which was dissolved in benzene and passed through a column of alumina. Elution with chloroform followed by evaporation of the chloroform gave a slightly colored product which when crystallized from benzene gave 1 g. of 4-acetylamino-2-fluorobiphenyl, m.p. 146.5-147.5°.

Anal. Calcd. for $C_{14}H_{12}ONF$: C, 73.31; H, 5.28. Found: C, 73.61; H, 5.24.

2-Fluorobiphenyl. - Thirty-eight grams of sodium nitrate dissolved in 150 ml. of water was added dropwise to a solution of 85 g. of 2-aminobiphenyl in 100 ml. of concentrated hydrofluoric acid at 5°. To this solution was added 100 ml. of fluoboric acid(34 g. of boric acid in 92 g. of 48% hydrochloric acid) and the heavy precipitate was stirred for .5 hour. The precipitate was filtered, washed with cold water, methanol and ether. The 2-biphenyldiazonium fluoborate was decomposed at room temperature and the product was distilled with steam. Crystallization from alcohol gave 45 g. of 2-fluorobiphenyl, m.p. 74° [10].

4'-Acetyl-2-fluorobiphenyl. - A solution of 107 g. of 2-fluorobiphenyl in 250 ml. of carbon disulfide was placed in a 1 liter 3-necked flask fitted with a mechanical stirrer, dropping funnel and a reflux condenser with a gas trap. To the solution was added 188 g. of aluminum chloride. The mixture was heated on a steam bath till gentle refluxing began and 51 g. of acetic anhydride was added slowly through the dropping funnel. Time for addition was 1 hour, followed by 1 hour of refluxing. Most of the solvent was removed by distillation and the residue was poured into an ice-hydrochloric acid solution. The mixture was extracted with ether, washed with water, 10% sodium hydroxide and water, and dried. The ether was evaporated and the residue was crystallized from 100 ml. of hexane and 100 ml. of benzene to give 70 g. of 4'-acetyl-2-fluorobiphenyl, m.p. 85-86.5° [10]. A second crop of 30 g. was obtained by concentrating the mother liquors.

2-Fluoro-4'-biphenylcarboxylic Acid. - A solution of 109 g. of sodium hydroxide in 150 ml. of water in a 2 liter 3-necked flask was cooled to room temperature. To this solution was added 625 g. of ice, and chlorine gas was passed rapidly through the solution until 80 g. had been absorbed. The flask was fitted with a thermometer, stirrer, and a condenser. A solution of 54 g. of 4'-acetyl-2-fluorobiphenyl in 200 ml. of dioxane

was added and the mixture was heated to 80°. As soon as the chloroform began to reflux, the mixture was cooled in an ice bath to keep the reaction under control. Heat was applied to keep the chloroform gently refluxing for two hours. The reaction mixture was cooled and the excess chlorine was destroyed with 25 g. of sodium bisulfite in 100 ml. of water. The solution was poured into a 2 liter beaker and acidified with about 100 ml. of concentrated hydrochloric acid. The white precipitate was filtered giving 51 g. of 2-fluoro-4'-biphenylcarboxylic acid, m.p. 222-224°[5].

Nitration of 2-Fluoro-4'-biphenylcarboxylic Acid. - Fifty grams of 2-fluoro-4'-biphenylcarboxylic acid was added in small portions to a mixture of 50 ml. of concentrated nitric acid in 300 ml. of concentrated sulfuric acid in a 2 liter round bottom flask. The temperature was kept between 30-35°. After the addition, the reaction mixture was kept at room temperature overnight. It was then poured into 2000 g. of ice and filtered. The precipitate was dissolved in ether, washed with water and dried. The ether was evaporated to 100 ml. and 500 ml. of benzene was added. Further evaporation removed most of the ether and 45 g. of 2(?),5'(?)-dinitro-2'-fluoro-4-biphenylcarboxylic acid, m.p.192-193°.

Anal. Calcd. for $C_{13}H_7O_6N_2F$: C, 49.51; H, 2.31. Found: C, 49.47; H, 2.71.

All attempts to decarboxylate this acid failed.

4'-Acetylamino-2-fluorobiphenyl

Oxime of 4'-Acetyl-2-fluorobiphenyl. - Twenty grams of 4'-acetyl-2-fluorobiphenyl, 10 g. of hydroxylamine sulfate, 10 g. of sodium hydroxide, 125 ml. of water and 50 ml. of alcohol were heated until solution occurred. On cooling 21.5 g. of crude oxime, m.p. 143-147° was obtained. Recrystallization from alcohol gave 19 g. m.p. 147-148°.

Anal. Calcd. for $C_{14}H_{12}ONF$: C, 73.31; H, 5.24. Found: C, 73.26; H, 5.50.

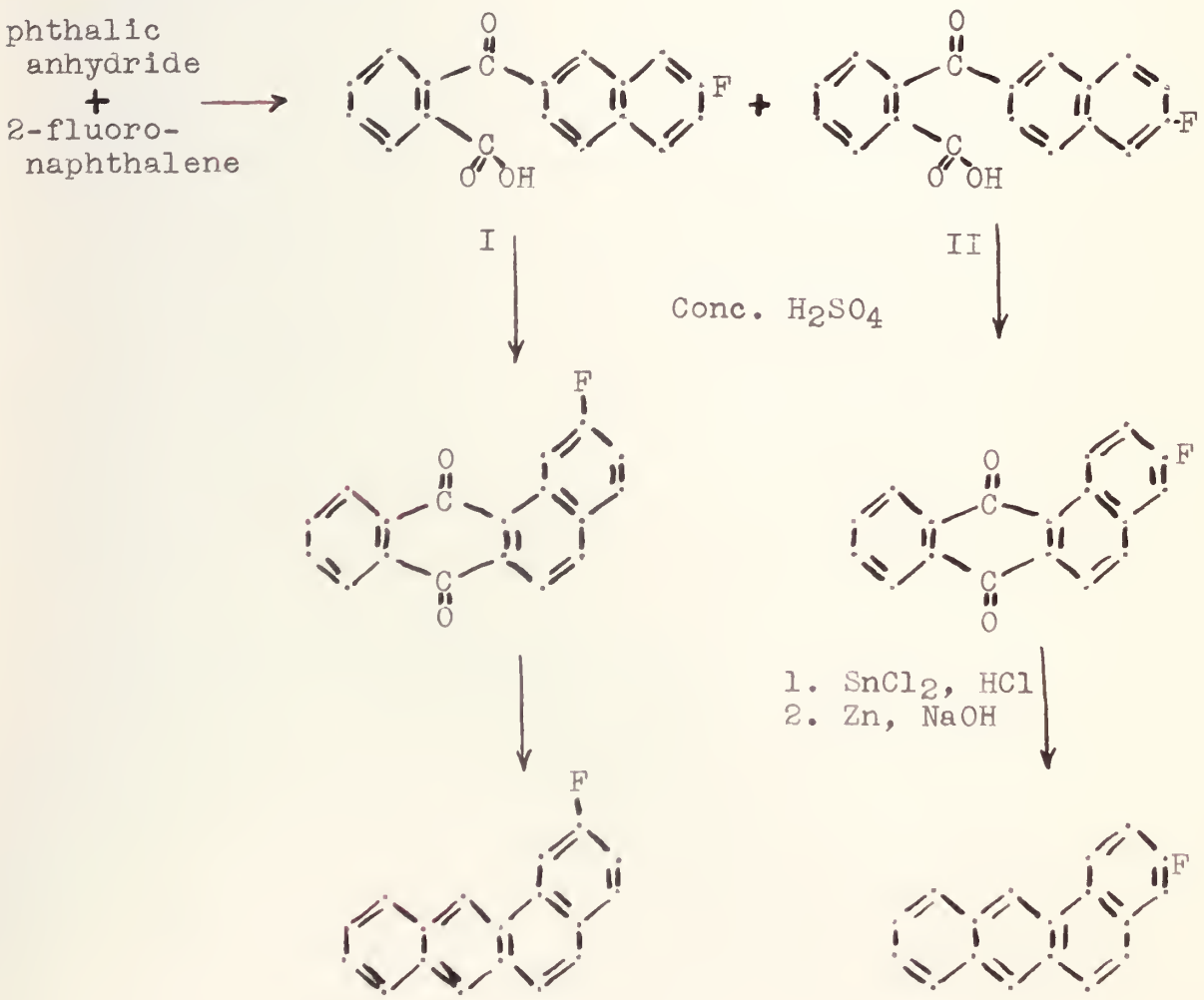
Beckmann Rearrangement of the Oxime of 4'-Acetyl-2-fluorobiphenyl. - Seventeen grams of the oxime was dissolved in 50 ml. of anhydrous ether and 4.5 g. of phosphorous pentachloride was added slowly. The mixture was refluxed for 15 minutes and then cooled. The phosphorous pentachloride was decomposed by the addition of water and the ether was removed by evaporation, leaving a solid residue. This residue was hydrolized by heating 1 hour with 200 ml. of alcohol, 100 ml. of water and 100 ml. of concentrated hydrochloric acid. Another 200 ml. of concentrated hydrochloric acid was then added and refluxing was continued for another hour. Evaporation of the alcohol caused 15 g. of the hydrochloride of 4'-amino-2-fluorobiphenyl to precipitate.

4'-Acetylamino-2-fluorobiphenyl. - 4'-amino-2-fluorobiphenyl was acetylated by the procedure of Fieser[13] to give 4'-acetylamino-2-fluorobiphenyl, m.p. 157-158°.

Anal. Calcd. for $C_{14}H_{12}ONF$: C, 73.31; H, 5.24. Found: C, 73.23; H, 5.56.

2- and 3-FLUOROBENZ[a]ANTHRACENE

Badger[14] has prepared 2- and 3-chlorobenz[a]anthracene from 2-chloronaphthalene and phthalic anhydride. A similar procedure was used to prepare 2- and 3-fluorobenz[a]anthracene from 2-fluoronaphthalene and phthalic anhydride. The following series illustrates the procedure used.



Badger[14] found that of the isomeric chloro acids, 2-(7-chloro-2-(1?)-naphthoyl)benzoic acid was formed in the larger amount. Assuming that fluorine has the same directive influence as chlorine, then the acid formed in the larger amount in this case would be 2-(7-fluoro-2-(1?)-naphthoyl)benzoic acid I.

EXPERIMENTAL

2-Fluoronaphthalene. - To a solution of 124 ml. of 6N hydrochloric acid was added 35.8 g. of 2-naphthylamine. The paste like mixture was cooled to 0° and 17.3 g. of sodium nitrite was added dropwise. The temperature was kept below 10° during the addition. After the diazotization was complete, a solution of cold fluoboric acid (21 g. of boric acid and 57 g. of 48% hydrofluoric acid) was added in one portion. The thick paste was stirred for 30 minutes. It was then filtered and the solid diazonium fluoborate was washed with cold dioxane and cold ether. The diazonium fluoborate, 50 g., was air dried and then decomposed with heat in a large flask with a large tube leading up a good fume hood. The black tarry residue was steam distilled giving 17 g. of white 2-fluoronaphthalene, m.p. 57-59°.

2-(6-and 7-Fluoro-2-(1?)-naphthoyl)benzoic Acids. - Twenty-two grams of 2-fluoronaphthalene, 22 g. of phthalic anhydride were dissolved in 200 ml. of s-tetrachloroethane in a 500 ml. 3-necked flask fitted with a mechanical stirrer. To this solution at 0° was added 44 g. of anhydrous aluminum chloride. The reaction was kept at 0° for 3 hours, then at room temperature for 24 hours and finally heated on a steam bath for 1 hour. The mixture was decomposed on cracked ice in the

presence of hydrochloric acid and then the s-tetrachloroethane was removed by steam distillation. The solid residue was filtered, dissolved in sodium hydroxide, filtered and precipitated with hydrochloric acid. Combined yield of the isomeric acids was 31 g. (80%).

Separation of the isomers. - Separation of the isomers was gained mainly by fractional crystallization using the solvents acetic acid and benzene. 2-(7-Fluoro-2(1?)-naphthoyl)benzoic acid was obtained pure by this procedure. Distinct crystals of 2-(6-fluoro-2(1?)-naphthoyl)benzoic acid were formed during some of the crystallizations. These were separated and were recrystallized to give the pure acid. The mixed isomers left in the mother liquors were then changed to the quinone for further separation.

The 2-(6-fluoro-2(1?)-naphthoyl)benzoic acid melted at 206-207°.

Anal. Calcd. for $C_{18}H_{11}O_3F$: C, 73.48; H, 3.77. Found: C, 73.10; H, 3.96.

The 2-(7-fluoro-2(1?)-naphthoyl)benzoic acid melted at 197-198°.

Anal. Calcd. for $C_{18}H_{11}O_3F$: C, 73.48; H, 3.77. Found: C, 73.80; H, 3.98.

An attempt was made to separate the isomers through the formation of the acetoxy lactones of the acids. Separation was successful in only one instance. Five grams of the mixed acids, m.p. 165-180° were dissolved

in 45 ml. of pyridine and 18 ml. of acetic anhydride and the solution was heated on a steam bath for 2 hours. The product was poured into water and the gum which separated was fractionally crystallized from alcohol. The acetoxy lactone, m.p. 179-180° (2 g.) gave 2-(6-fluoro-2(1?)-naphthoyl)benzoic acid on hydrolizing with dilute base. The acetoxy lactone, m.p. 123-125° (1 g.) gave 2-(7-fluoro-2(1?)-naphthoyl) benzoic acid on hydrolysis.

2-Fluorobenz[a]anthracene-7,12-dione. - Eight grams of 2-(7-fluoro-2(1?)-naphthoyl)benzoic acid was dissolved in 80 ml. of concentrated sulfuric acid. This solution was heated on a water bath at 70° for 6 hours. The product was decomposed by pouring the solution onto 400 g. of cracked ice. The yellow precipitate was filtered and recrystallized from 100 ml. of glacial acetic acid to give 6 g. (75%) of 2-fluorobenz[a]anthracene-7,12-dione, m.p. 196-197°.

Anal. Calcd. for $C_{18}H_9O_2F$: C, 78.25; H, 3.28. Found: C, 78.01; H, 3.47.

3-Fluorobenz[a]anthracene-7,12-dione. - The residue from the mother liquors left from the acid separation was treated in the same manner as in the preparation of 2-fluorobenz[a]anthracene-7,12-dione. After several recrystallizations from glacial acetic acid pure

3-fluorobenz[a]anthracene-7,12-dione was obtained, m.p. 192-193°.

Anal. Calcd.for $C_{16}H_9O_2F$: C, 78.25; H, 3.28. Found: C, 78.45; H, 3.41.

2-Fluorobenz[a]anthracene. - Five grams of 2-fluorobenz[a]anthracene-7,12-dione, 6 g. of stannous chloride were dissolved in 100 ml. of glacial acetic acid. To this mixture was added 10 ml. of concentrated hydrochloric acid and the mixture was refluxed with stirring for 2 hours. The product was poured over cracked ice and the brown precipitate filtered and air dried. This product was refluxed in 100 ml. of 10% sodium hydroxide in the presence of 10 g. of zinc dust for 3 hours. The mixture was never homogeneous. The product was extracted with benzene, washed with water, concentrated sulfuric acid and dried over anhydrous sodium sulfate. Evaporation of the solvent gave 3.5 g. (75%) of 2-fluorobenz[a]anthracene which when recrystallized from benzene-alcohol had a m.p. of 176-177°.

Anal. Calcd. for $C_{18}H_{11}F$: C, 87.80; H, 4.50. Found: C, 87.64; H, 4.60.

Picrate, m.p. 132-133°.

Anal. Calcd. for $C_{24}H_{14}O_7N_3F$: C, 60.64; H, 2.97. Found: C, 60.80; H, 2.92.

3-Fluorobenz[a]anthracene. - This was prepared in the same manner as the 2-fluoro isomer with the following modifications. In the stannous chloride and hydrochloric acid reduction, 300 ml. of glacial acetic acid was needed to dissolve the reactants. The product, 3-fluorobenz[a]anthracene, m.p. 169-170° was recrystallized from benzene-hexane.

Anal. Calcd. for $C_{18}H_{11}F$: C, 87.80; H, 4.50. Found: C, 87.46; H, 4.57.

2-ACETYLAMINOPHENANTHRENE

Werner[15] reported the preparation of 2-acetylaminophenanthrene from 2-hydroxyphenanthrene by heating a mixture of 2-hydroxyphenanthrene, sodium acetate, ammonium chloride and acetic acid for 9 hours at 280-300°. Bachmann[16] prepared it by doing a Beckmann rearrangement on the oxime of 2-acetylphenanthrene[17]. 2-Acetylaminophenanthrene was prepared in this laboratory by a Schmidt reaction on 2-acetylphenanthrene. A yield of 56% was obtained.

EXPERIMENTAL

2 and 3-Acetylphenanthrenes. - One hundred and thirty-two grams of anhydrous aluminum chloride was added in small portions to 600 g. of freshly distilled nitrobenzene and the resulting clear solution was mixed with a solution of 80 g. of phenanthrene in 240 g. of nitrobenzene, in a three necked flask. The mixture was cooled in an ice bath and cold freshly distilled acetyl chloride was added all at once. The mixture was stirred at ice water temperature for one-half hour and then at room temperature overnight. The viscous tar was poured into 500 g. of ice and 80 ml. of concentrated hydrochloric acid. The nitrobenzene was removed with steam and the black residue was dissolved in chloroform washed with water and dried with anhydrous sodium sulfate. The chloroform solution was vacumn distilled giving a mixture of the acetylphenanthrenes, b.p. 180-210°(1mm.) The distillate was poured into 500 ml. of ether with stirring and the 2-acetylphenanthrene precipitated. Recrystallization from methanol gave 14 g., m.p. 142-143°[17].

The ether solution was evaporated to give the crude 3-acetylphenanthrene.

2-Acetylaminophenanthrene. - Five grams of 2-acetylphenanthrene was dissolved in 100 ml. of chloroform and 6 ml. of concentrated sulfuric acid. To this

mixture at 20° was added dropwise 50 ml. of 1 M. hydrazoic acid in benzene solution. The reaction was immediate and the 2-acetylaminophenanthrene precipitated to the walls of the flask. After the evolution of nitrogen had ceased(about 1 hour) the solvent was poured off and the product was washed into water, and filtered. Recrystallization from xylene-acetone gave 3 g. (56%) m.p. 225-226° [15].

SUMMARY

The five isomeric monofluoro-4-acetylaminobiphenyls were synthesized. All but 2-fluoro-4-acetylaminobiphenyl were prepared in sufficient quantities for biological tests. Another method of synthesis for the preparation of 2-fluoro-4-acetylaminobiphenyl is being attempted.

2 and 3-Fluorobenz[a]anthracene were prepared. These were not characterized but structures were assigned to them by comparison of the observed properties with those of the corresponding chloro compounds reported by Badger[13].

2-Acetylaminophenanthrene was prepared from 2-acetylphenanthrene by a Schmidt reaction.

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PART II

THE SYNTHESIS OF SOME CYCLIC IODONIUM SALTS

INTRODUCTION

Ring closures using dihalogenated aromatic compounds to give biphenylene have proved successful in several instances. Lothrup[1] found that biphenylene can be prepared by heating either 2,2'-dibromobiphenyl or biphenyleneiodonium iodide with cupric oxide. Cava[2] prepared 1,2-benzobiphenylene by heating 1-(2-iodophenyl)-2-iodonaphthalene.

An indirect procedure for ring closure from 2,2'-diiodobiphenyl through the intermediate formation of biphenylyl mercury has been reported by Wittig[3]. The biphenylyl mercury when heated with silver powder yields biphenylene.

The standard method for the preparation of the dihalogenated aromatic compounds and cyclic iodonium salts used for these ring closures is tetrazotization of the corresponding diamine followed by treatment with potassium iodide. Varying proportions of the diiodide and the cyclic iodonium iodide are obtained from this reaction.

Biphenylene iodonium iodide when heated gives 2,2'-diiodobiphenyl. A convenient method for the preparation of suitable diiodo compounds to be used for ring closures giving 4,5,6 and 7 membered rings would

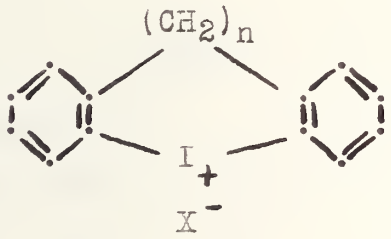
be through the formation of cyclic iodonium salts having 5,6,7 and 8 membered rings.

Beringer[4] has recently developed a method for the preparation of iodonium salts in high yields. He has shown that an iodoso compound will condense with an aromatic compound in the presence of sulfuric acid to yield an iodonium salt. According to Beringer, it seems likely that the reaction mechanism involves electrophilic substitution by the action of sulfuric acid on the conjugate acid formed by the iodoso compound.

Several cyclic iodonium salts have been prepared by a modification of the method of Beringer.

CYCLIC IODONIUM SALTS

J. Collette[5], of this laboratory, prepared several cyclic iodonium salts corresponding to I where n=0,1 and 3 from o-iodobiphenyl, 1-(o-iodophenyl)-phenylmethane and 1-(o-iodophenyl)-3-phenylpropane respectively.



I

By a similar procedure, several cyclic iodonium salts corresponding to I with n=2 were prepared from 1-(o-iodophenyl)-2-phenylethane II. In this procedure the iodo compound was oxidized with peracetic acid to the iodoso compound[6]. The addition of concentrated sulfuric acid to the iodoso compound in acetic anhydride solution brought about a facile ring closure to give a cyclic iodonium salt. Other salts were easily prepared due to large differences of their solubility in water.

II was prepared from 1-(o-aminophenyl)-2-phenylethane[7] by diazotization followed by subsequent treatment with potassium iodide.

Table I indicates some of the properties of the

cyclic iodonium salts prepared in this laboratory. The stability of these salts as indicated by their melting points(decomposition points) and yield is probably related to the bond angle deformation which is calculated in the last column of the table. I with n 2 shows the greatest internal stress and thus the least stability.

TABLE I

I	M.P.(decomp. pt.)			Yield	Bond angle deformation in the cation
	Chloride	Bromide	Iodide		
n=0	292-4	254-5	215	99	1.5°
n=1	244-5	222-4	184-5	95	10.5°
n=2	148-9	150-2	144-5	60	19.0°
n=3	180-1	170-5	145-9	70	16.5°

EXPERIMENTAL

1-(o-Iodophenyl)-2-phenylethane. - 1-(o-Aminophenyl)-2-phenylethane[7] was diazotized in the usual manner and the diazonium solution was treated with potassium iodide. The product which separated as an oil was steam distilled, extracted with ether and distilled under reduced pressure. The yield of 1-(o-iodophenyl)-2-phenylethane, b.p. 175° at .5 m.m. was 50%.

Anal. Calcd. for $C_{14}H_{13}I$: I, 41.20.
Found: I, 40.96, 40.84.

Peracetic Acid Oxidation and Cyclization. - All preparations and reactions with organic peracids should be carried out behind a safety shield.[8] A solution of peracetic acid was made by the slow addition of 25 ml. of 25-30% hydrogen peroxide to 100 ml. of cold acetic anhydride. The mixture was kept cold in an ice-water bath until it became homogeneous at which time the solution was allowed to stand overnight at room temperature. A solution of 5 g. of 1-(o-iodophenyl)-2-phenylethane in 10 ml. of acetic anhydride was added to 25 ml. of the peracetic acid solution and allowed to stand at room temperature for 12 hours. The reaction mixture which now contained the iodoso compound was cooled in an ice-water bath, and to the cold stirred solution there was added dropwise 5.0 ml. of sulfuric

acid. The reaction mixture became dark and after standing for 6 hours at room temperature was diluted with 100 ml. of water. A dark tarry material separated on standing. The mixture was filtered and the filtrate was saturated with sodium chloride. A white precipitate of the iodonium chloride formed and was filtered and recrystallized from water, m.p. 148-149°(dec).

Anal. Calcd.for $C_{14}H_{12}ClI$: Cl, 9.87.
Found: Cl, 10.40, 10.47.

A solution of the iodonium chloride in water was treated with potassium bromide or iodide to yield the iodonium bromide and the iodonium iodide.

The bromide melted at 150-152° (dec.).

Anal. Calcd. for $C_{14}H_{12}BrI$: Br, 20.67.
Found: Br, 21.19.

The iodide melted at 144-145°(dec.).

Anal. Calcd. for $C_{14}H_{12}I_2$; I, 29.02.
Found: I, 29.08.

SUMMARY

Several cyclic iodonium salts were synthesized by a modification of the method of Beringer[4]. The cyclizations occurred readily and in good yields. The stability of these compounds seemed to be related to the bond angle deformation in the iodonium ring.

The use of these compounds for studies of carbon to carbon ring closures seems justified.

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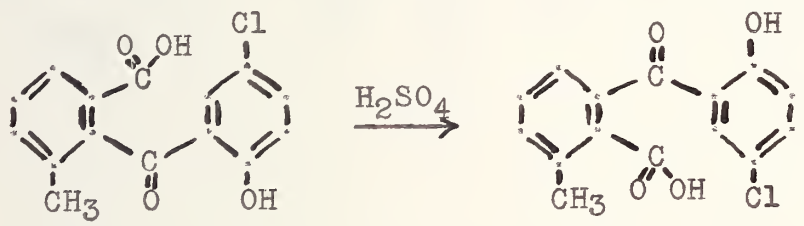
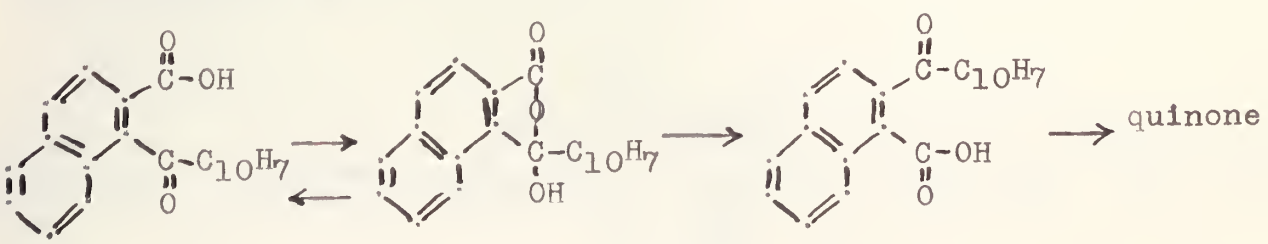
PART III

THE HAYASHI REARRANGEMENT OF o-BENZOYLBENZOIC ACIDS

Hayashi[1], in 1927, was the first to report the occurrence of a molecular rearrangement in the course of the ring closure of certain substituted o-benzoyl benzoic acids.

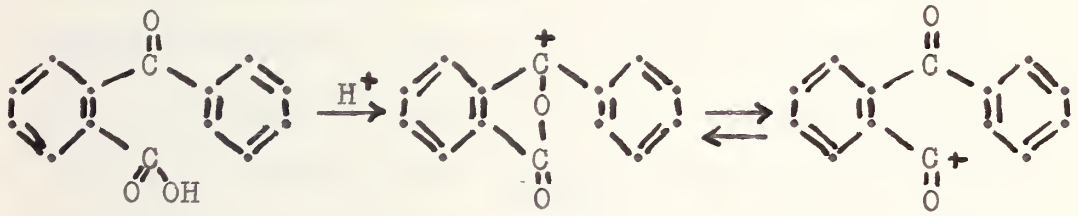


Several other instances of this type of a rearrangement have been reported in the literature[2]. Cook found that cyclization of 1-(1-naphthoyl)-2-naphthoic acid(I) gave 1,2,5,6-dibenzanthraquinone rather than the expected 1,2,7,8-dibenzanthraquinone. Cook suggested that rearrangement proceeded through the hydroxy lactone of the keto acid[3].



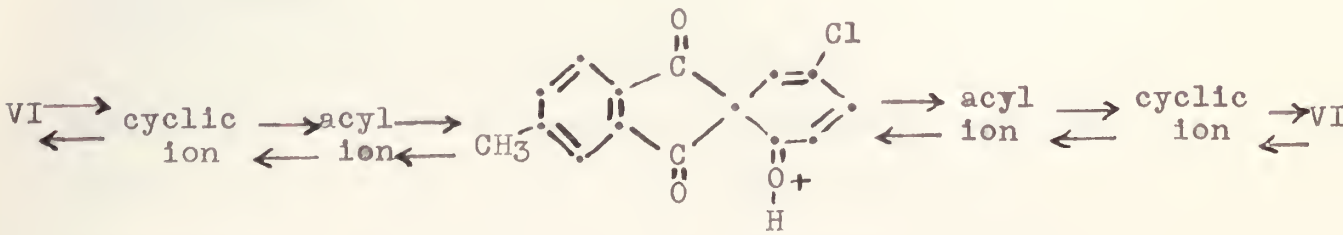
I

Newman[4], has studied the behaviour of o-benzoyl benzoic acid in the solvent sulfuric acid and has found that intramolecular acylation occurs through the cyclic carbonium ion (II) which on heating cleaves to yield the acyl carbonium ion (III).



II III

A mechanism for the Hayashi rearrangement should therefore involve rearrangement of the acyl carbonium ion. Using the reversible change between 2-(5'-chloro-2'-hydroxybenzoyl)-4-methylbenzoic acid (VI) and 2-(5'-chloro-2'-hydroxybenzoyl)-5-methylbenzoic acid (VII) reported by Hayashi[2a], a possible mechanism would be through the non-classical "phenonium" cationic type structure IV.



IV

Evidence for and against the formation of an "ethyleneonium" cationic intermediate in carbonium ion type reactions has been reported by Winstein[5], Cram[6], Roberts[7] and Collins[8]. Reaction rates and stereochemical techniques were used and where these were not applicable Roberts[7] and Collins[8] obtained valuable information from the isotopic tracer technique. No experimental evidence to indicate the role of IV in the Hayashi rearrangement was found. It is possibly just a transition state through which acyl carbonium ions are interconverted.

It is significant that Hayashi[2a] found that 2-benzoyl-5-methylbenzoic acid did not rearrange in concentrated sulfuric acid at room temperature whereas 2-(5'-chloro-2'-hydroxybenzoyl)-5-methylbenzoic acid rearranged under the same conditions. Similarly, Goncalves[2e] found that the rearrangement of 2-(2-thenoyl)-6-nitrobenzoic acid and 2-(2-thenoyl)-4-nitrobenzoic acid could be affected in boiling acetic acid but even more satisfactorily by the action of warm concentrated sulfuric acid.

In the present work, it has been found that 2-benzoyl-4-methoxybenzoic acid does not rearrange in concentrated sulfuric acid at 65° but instead undergoes ring closure. In contrast to this behaviour it has been found that 2-(4'-methoxybenzoyl)-4-methoxybenzoic acid(VIII) under the same conditions rearranges to

2-(4'-methoxybenzoyl)-5-methoxybenzoic acid (IX) without ring closure.

One possible interpretation of these observations is that the "phenonium" ion is stabilized by delocalization of the unshared electron pairs on the oxygen of the 4'-methoxyl and 2'-hydroxyl groups. Similarly the 2-thienyl group might be expected to be favorable because of its nucleophilic properties.

In all cases except VIII IX, we would expect the acyl carbonium ion of the product in the rearrangement to be the stable form in solution. In the case of VIII IX, it would appear that the cyclic carbonium ion is the stable form, possibly because of the two methoxyl groups in favorable positions.

EXPERIMENTAL

2-Benzoyl-4-methoxybenzoic Acid. - This compound was prepared by the method of Weizmann[9], who reported the compound to be 4(5?)-methoxy-2-benzoylbenzoic acid. Melby of this laboratory has characterized it to be 2-benzoyl-4-methoxybenzoic, m.p. 172°.

2-(4'-Methoxybenzoyl)-4-methoxybenzoic Acid (VIII). - The Grignard reagent from 18.7 g. of p-bromoanisole in 200 ml. of ether was added to a well stirred solution of 17.8 g. of 4-methoxyphthalic anhydride in 300 ml. of benzene. After refluxing for three hours, the reaction mixture was decomposed with 150 ml. of saturated ammonium chloride and 10 ml. of dilute hydrochloric acid. The ether-benzene solution of hydrolyzed reaction products was shaken with carbonate. The carbonate extract was acidified with acetic acid and yielded 11.5 g. of keto acid, m.p. 198-206°. After crystallization from benzene and from alcohol it melted at 210-211°.

Anal. Calcd. for $C_{16}H_{14}O_5$: C, 67.1; H, 4.9. Found: C, 67.05; H, 4.90.

The keto acid was characterized by heating with basic copper carbonate for one hour at 260°. This afforded the dimethoxy compound which was refluxed with 55 % hydriodic acid. The demethylated material was crystallized twice from water and yielded yellow crystals of 3',4-dihydroxybenzophenone, m.p. 196-198°.

2-(4'-Methoxybenzoyl)-5-methoxybenzoic Acid (IX). - The acetic acid acidified filtrate from the above keto acid was treated with hydrochloric acid. This gave 3.5 g. of keto acid, m.p. 165-173°. The acid was crystallized from benzene and alcohol and melted at 174-175°.

Anal. Calcd. for $C_{16}H_{14}O_5$: C, 67.1; H, 4.9. Found: C, 66.82; H, 4.96.

It was characterized by heating with basic copper carbonate yielded 4,4'-dimethoxybenzophenone, m.p. 144-145°.

Reactions of Keto Acids with Concentrated Sulfuric Acid. - The acid (1 g.) was dissolved in 6 ml. of concentrated sulfuric acid and heated at 65° for one hour at which time it was cooled and diluted with ice and water. The reaction mixture was made basic with sodium hydroxide and any cyclized material was separated. The filtrate was acidified to yield unchanged or rearranged keto acid. Under these conditions 2-benzoyl-4-methoxybenzoic acid afforded 0.8 g. of unchanged acid and 0.2 g. of 2-methoxyanthraquinone, m.p. 195°. Compound VIII (0.5g.) in 3 ml. of concentrated sulfuric acid at 65° for six hours gave 0.5 g. of IX, m.p.170-172°,and after crystallization from dilute alcohol afforded 0.45 g. of keto acid, m.p. 173-175°.

The following acids were found not to rearrange under the above conditions: 2-benzoyl-4-hydroxybenzoic acid, 2-benzoyl-5-hydroxybenzoic acid and 2-benzoyl-5-methoxy-

SUMMARY

A mechanism was proposed to explain the rearrangemetn of some substituted o-benzoylbenzoic acids in concentrated sulfuric acid. No direct evidence for the existence of the proposed non-classical "phenonium" ion was found but work is being done to show its existence or non-existence.

The compound reported by Weizmann[9] to be 4(5?)-methoxy-2-benzoylbenzoic acid was characterized to be 2-benzoyl-4-methoxybenzoic acid. The compounds, 2-(4'-methoxybenzoyl)-4-methoxybenzoic acid (VIII) and 2(4'-methoxybenzoyl)-5-methoxybenzoyl benzoic acid (IX) were synthesized. VIII was found to rearrange to IX in concentrated sulfuric acid.

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